PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 66797-394	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/38684	International filing date *(day/month/year)* 04 December 2003 (04.12.2003)	Priority date *(day/month/year)* 04 December 2002 (04.12.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 38/43; C12N 9/00 and US Cl.: 424/94.1, 94.6; 435/197		
Applicant APPLIED MOLECULAR EVOLUTION, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 02 July 2004 (02.07.2004)	Date of completion of this report 14 April 2005 (14.04.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer David J. Blanchard J. Roberts for Telephone No. (571) 272-1600

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I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-77 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 78-90 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-31 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-36, 48-104
The opinion as to Novelty was negative (No) with respect to claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 37-47
The opinion as to Inventive Step was positive (Yes)with respect to claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-36, 55, 57, 59, 61, 63, 65, 67, 97-104
The opinion as to Inventive Step was negative(NO) with respect to claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 37-54, 56, 58, 60, 62, 64, 66, 68-96
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-104
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

V. 2. Citations and Explanations:

Claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 37-47 lack novelty under PCT Article 33(2) as being anticipated by Sevigny et al.

The claims are drawn to butyrylcholinesterase variants and nucleic acids encoding butyrylcholinesterase variantscomprising one of the recited sequences or functional fragment thereof.

Sevigny et al teach the sequence of human butyrylcholinesterase variant having a single nucleotide polymorphism, which is interpreted as a functional fragment of the recited butyrylcholinesterase variant sequences (see Figures 2 and 4).

Claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 37-54, 56, 58, 60, 62, 64, 66 and 68-96 lack an inventive step under PCT Article 33(3) as being obvious over Sevigny et al in view of Morton et al.

The claims are drawn to butyrylcholinesterase variants and nucleic acids encoding butyrylcholinesterase variantscomprising one of the recited sequences or functional fragment thereof and a method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with said butyrylcholinesterase variant or functional fragment thereof and a method of treating cancer comprising administering an effective amount of a butyrylcholinesterase variant or functional fragment thereof, exhibiting increased capability to convert a camptothecin derivative to a topoisomerase inhibitor.

Sevigny et al have been described supra. Sevigny et al do not teach a method converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with said butyrylcholinesterase variant or functional fragment thereof and a method of treating cancer comprising administering an effective amount of a butyrylcholinesterase variant or functional fragment thereof, exhibiting increased capability to convert a camptothecin derivative to a topoisomerase inhibitor. These deficiencies are made up for in the teachings of Morton et al.
Morton et al teach the activation of the prodrug CPT-11 by butyrylcholinesterase, particularly equine butyrylcholinesterase, to generate SN-38, a potent topoisomerase I poison (see pages 1458 and 1460).

One of ordinary skill in the art at the time the invention was made would have been motivated to and had a reasonable expectation of success to use the butyrylcholinesterase functional fragment taught by Sevigny et al or a function fragment of the equine butyrylcholinesterase for converting CPT-11 (camptothecin derivative) to SN-38 (topoisomerase inhibitor) for the treatment of cancer in view of Morton et al because Morton et al teach that butyrylcholinesterase, particularly equine butyrylcholinesterase, converts CPT-11 to SN-38, which is a topoisomerase inhibitor and thus, effective for treating cancer.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-36, 55, 57, 59, 61, 63, 65, 67 and 97-104 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the butyrylcholinesterase variants comprising the recited sequences, or a method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with said butyrylcholinesterase variants, or a method of treating cancer comprising administering an effective amount of the recited butyrylcholinesterase variants, exhibiting increased capability to convert a camptothecin derivative to a topoisomerase inhibitor.

Claims 1-104 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.